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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/533,847	11/30/2005	Fyodor Urnov	8325-0034 (S34-US1)	7879

20855 7590 11/17/2009

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

MAIL DATE	DELIVERY MODE
11/17/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,847	URNOV ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1 and 6-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 August 2009* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application.
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 1 and 6-15 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 01 August 2007.

Drawings

2. New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because:

a. Figure(s) 1-6 are not properly labeled (note "Fig." v. >>FIG.<<). See 37 CFR 1.84(u)(1).

b. The lettering is not of proper size, uniform density, and well-defined in Figure(s) 1-6. See 37 CFR 1.84 (l) and (p)(1) – (5). ("Numbering, letters and reference characters must measure at least 0.32 cm (1/8 inch) in height.")

3. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

Replacement Drawing Sheets

Drawing changes must be made by presenting replacement sheets which incorporate the desired changes and which comply with 37 CFR 1.84. An explanation of the changes made must be presented either in the drawing amendments section, or remarks, section of the amendment paper. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). A replacement sheet must include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of the amended drawing(s) must not be labeled as "amended." If the changes to the drawing figure(s) are not accepted by the examiner, applicant will be notified of any required corrective action in the next Office action. No further drawing submission will be required, unless applicant is notified.

Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and within the top margin.

Annotated Drawing Sheets

A marked-up copy of any amended drawing figure, including annotations indicating the changes made, may be submitted or required by the examiner. The annotated drawing sheet(s) must be clearly labeled as "Annotated Sheet" and must be presented in the amendment or remarks section that explains the change(s) to the drawings.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in ABANDONMENT of the application.

If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings MUST be filed within the THREE MONTH shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 2-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. As a result of amendment filed 26 May 2009, claims 2-5 are now limited to an array of polynucleotides sequences with "the polynucleotide sequences consisting of accessible regions of cellular chromatin." A review of the response fails to locate where applicant has indicated support for this limitation in the original disclosure. See MPEP 714.02 [R-3]. Further, a review of the original disclosure fails to find support for the newly-added limitation. Accordingly, the limitation that the only nucleic acids present on the array are those of accessible regions is deemed to constitute new matter.

Response to argument

At page 7, bridging to page 9, of the response of 31 August 2009, argument is presented that the claimed invention, including newly-added limitations, is supported by the disclosure. Attention is directed to "page 2, lines 18-21; page 3, lines 7-11; page 12, lines 26,33; page 36, lines 3-5; page 37, lines 30-32; page 40, lines 13-16; page 40, line 31 to page 41, line 3; [and] page 49, lines 2-3."

Applicant's argument, including the cited passages, have been considered and have not been found persuasive towards the withdrawal of the rejection. While agreement is reached in that applicant, at the time of filing, did contemplate an array of nucleic acids, the record does not

support the position that the array envisioned is one "consisting of accessible regions of cellular chromatin" (claim 2, preamble; emphasis added). Rather, the disclosure provides support for "an array comprising a plurality of accessible polynucleotide sequences, wherein: (a) the sequences are isolated based on their accessibility in cellular chromatin; and (b) each accessible sequence is located at a distinct address on a solid support" (specification at page 3, lines 7-10; emphasis added). A review of the record, including the cited passages fails to identify where applicant contemplated assembling an array that consists of only nucleic acid that corresponds to an "accessible region" of cellular chromatin. Accordingly, and in the absence of convincing evidence to the contrary, the rejection of claims as it relates to the inclusion of new matter is maintained.

7. As a result of amendment filed 26 May 2009, claims 2-5 are now limited to an array of polynucleotides sequences with "the polynucleotide sequences consisting of accessible regions of cellular chromatin." A review of the disclosure finds that a Sequence Listing was filed on 17 November 2005. Said Sequence Listing, however, has been found to comprise but a single sequence, and then the sequence depicted is that of 25 amino acids of an indeterminate composition, not of multiple nucleic acids that are derived from "accessible regions of cellular chromatin and are isolated based on their altered reactivity to probe of chromatin structure." For convenience, the sole disclosed sequence is reproduced below.

```
<400> SEQUENCE: 1
      Cys Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
      1               5                  10                  15
      Xaa Xaa His Xaa Xaa Xaa Xaa Xaa His
                  20                  25
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8. While the claimed invention is defined in terms of the process used to isolate it, and not in terms of its nucleotide structure, the specification similarly fails to describe the composition of the probe(s) that are used to isolate the members of the array.

9. As presently worded, the claimed array can comprise "available" nucleic acids that are derived from any life form as well as variants of same. In support of this position, attention is directed to page 8, last paragraph, of the specification, which states in part:

> Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated.

10. A review of the disclosure fails to find where any array of any nucleic acids, real or prophetic, has been prepared, regardless of the accessibility of the nucleotide sequence.

11. For purposes of examination, the array of polynucleotide sequences has been construed as encompassing at the very least, two nucleic acids molecules. A review of the disclosure has fails to identify where applicant has prepared any array, including an array that has two nucleic acids molecules, be they accessible or not.

12. While the specification explicitly allows for the inclusion of variants, the specification has not been found to provide an adequate written description of those nucleic acid molecules that are useful versus those that are not.

13. The absence of an adequate written description for any such array does not reasonably suggest that applicant had possession of the array at the times of filing.

14. It is noted that the members of the array are defined in terms of their being "accessible" to a "probe," however the claims do not specify the conditions under which the probe is to interact, and more particularly, they do not delineate those conditions under which the "bulk

DNA" cannot interact with the probe so as to thereby import some structure-function relationship. Further, the nucleic acid members of the array are not defined in terms of their corresponding to any particular gene(s), regulatory sequences, etc., so that some alternative means of importing a structure-function relationship. The presence of some clear and concise language identifying the nucleic acid members, the disclosure does not provide an adequate written description of the invention or reasonably suggest that applicant had possession of the entire genus of molecules encompassed by the present claims.

15. The case at hand is analogous to *Fiers v. Sugano* 25 USPQ2d 1604-5 (CAFC, January 1993) wherein is stated:

> We also reject *Fiers* argument that the existence of a workable method for preparing a DNA establishes conception of that material. Our statement in *Amgen* that conception may occur, *inter alia*, when one is able to define a chemical by its method of preparation requires that the DNA be claimed by its method of preparation. We recognize that, in addition to being claimable by structure or physical properties, a chemical material can be claimed by means of a process. A product-by-process claim normally is an after-the-fact definition, used after one has obtained a material by a particular process. Before reduction to practice, conception only of a process for making a substance, without a conception of a structural or equivalent definition of that substance, can at most constitute conception of the substance claimed as a process. Conception of a substance claimed *per se* without reference to a process requires conception of its structure, name, formula, or definitive chemical or physical properties. . .
> * * * *
> The difficulty that would arise if we were to hold that a conception occurs when one has only an idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions.

16. It appears that applicant is attempting to satisfy the written description requirement of 35 USC 112, first paragraph, through obviousness. Obviousness, however, cannot be relied upon for satisfaction of the written description requirement. In support of this position, attention is directed to the decision in *University of California v. Eli Lilly and Co.* (Fed. Cir. 1997) 43

USPQ2d at 1405, citing *Lockwood v. American Airlines Inc.* (Fed. Cir. 1997) 41 USPQ2d at 1966:

> Recently, we held that a description which renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.

17. For the above reasons, and in the absence of convincing evidence to the contrary, claims 2-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Response to argument

18. At page 10 of the response argument is presented that applicant generated "40,000 - 50,000 clones" (specification at page 62). This argument has been considered and has not been found persuasive. A review of the disclosure finds that applicant generated a library on an undisclosed number of fragments, and that the cloning of the fragments into a plasmid resulted in the generation of some 40,000 – 50,000 clones. These 40,000 – 50,000 sequences were not positioned on an array. Rather, applicant selected a sample of but 10 clones that were not randomly fractionated and which exhibited DNase I hypersensitivity. These clones were then mapped to the human genome, which found that 10% of the clones did not map to a DNase I hypersensitivity site in the human genome.

19. The invention under consideration is not directed to a method, but rather, to an array of nucleic acids. The aspect of generating a library, and then establishing clonal colonies of some, and method of mapping some 10 clones of human sequences does not support the position of an adequate written description of the array members, or that applicant had possession of the multitude of arrays encompassed by the claims.

20. At page 10 of the response applicant asserts: "The written description in this case does not require a listing of the precise sequence of any of the accessible region-containing clones. Rather, all that is required is that the specification evince possession of the polynucleotides forming the claimed arrays."

21. The above argument has been considered and has not been found persuasive. As set forth above in *Fiers*, "The difficulty that would arise if we were to hold that a conception occurs when one has only an idea of a compound, defining it by its hoped-for function, is that would-be inventors would file patent applications before they had made their inventions and before they could describe them. That is not consistent with the statute or the policy behind the statute, which is to promote disclosure of inventions." In the present case, the difficulty is even greater as the product is not defined in terms of having any particular function. Rather, it is defined as simply being from an "accessible region" of "cellular chromatin."

The case at hand is analogous to *University of California v. Eli Lilly and Co.* (CA FC, July 1997) 43 USPQ2d 1398 wherein is stated:

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what it achieves as a result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. *See In re Wilder*, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the

> invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.
>
> Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes, but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

22. In the present case applicant is claiming a broad category of nucleic acids, which can come from multiple organisms and from different cell types in different organisms. The claims and disclosure only define and describe the invention in terms of how it is to function- it is probe-accessible cellular chromatin. Many such genes, and/or their regulatory sequences/regions may achieve that result. Applicant's claiming of probe-accessible chromatin is analogous to one claiming cDNA. "Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." *Ibid.*

23. For the above reasons, and in the absence of convincing evidence to the contrary, claims 2-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

24. Claims 2-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

25. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' "Genentech, *Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary

The quantity of experimentation necessary is great, on the order of several man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims.

The amount of direction or guidance presented,

The amount of guidance provided is limited, generally prophetic, and not commensurate with the scope of the claims. The specification does not set forth any array, much les a method of using same.

The presence or absence of working examples

The specification comprises the following examples:

- Example 1: Preparation of regulatory DNA library from HEK 293 cells, pp. 61-62. In this example, total nuclear DNA was isolated, restricted, and inserted into a plasmid. Applicant reports that 40,000 – 50,000 clones were obtained.
- Example 2, Analysis of Selected Clones, pp. 62-66. 1% of the clones from Ex. 1 were evaluated.
- Example 3: Identification of target sequences of Estrogen Receptor (ER), pp. 66-67; and
- Example 4: Analysis of Drug Effects, pp. 67-68. DNA from estrogen treated and untreated cells were hybridized to regDNA chips. The composition, source and manner of making the chips are not disclosed.

None of the examples is directed to the identification of nucleic acid molecules that corresponds to accessible regions of cellular chromatin and is isolated based on their altered reactivity to probe of chromatin structure, and which are each individually isolated and bound to a distinct address on a solid support.

It is further noted that none of the examples teach how the claimed array is to be used in a method that has utility. While the elected invention is drawn to an array and not to a method of use, the specification must still enable the making and use of the invention. In the present case, the specification has not been found to do either. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> "'[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200,

> 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
>
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

The nature of the invention and the breadth of the claims

The invention relates generally to arrays of nucleic acids where each nucleotide sequence is located at a distinct address on a solid support. The nucleic acids are characterized in that, they correspond to accessible regions of cellular chromatin and are isolated based on an unspecified altered reactivity to probing of chromatin structure.

The members of the array can be of virtually any length, and at any density.

The array fairly encompasses nucleic acids that are derived from any life form.

The state of the prior art and the predictability or unpredictability of the art

The art to which the invention relates, *i.e.*, nucleic acid array art and hybridization art, has advanced to the point that certain problematic areas have been identified. In support of this position as it relates to the manufacture and use of oligonucleotide arrays, US Patent 6,077,674 (Schleifer et al.) addresses certain highly problematic areas:

> While in situ synthesis is a very flexible means for producing DNA arrays, the fidelity or percentage of full-length oligonucleotides synthesized within a feature on the array is less than 100 percent. An ideal array will have only full-length oligonucleotides attached to each feature. The ideal array promotes accuracy in hybridization experiments or assays or target biological materials. If the fidelity of an in situ generated array is less than 100 percent, it typically has non full-length oligonucleotides within a feature that usually consists of shorter lengths of the correct sequence, and to a lesser degree, incorrect sequences. Typical DNA coupling efficiencies are around 97 to 99 percent for the standard phosphoramidite chemistry. For oligonucleotides that are 25 nucleotides in length, these efficiencies result in only 46 to 77 percent full-length oligonucleotides contained within a feature (0.97^{25} to 0.99^{25}). This loss of fidelity can cause chemical noise in hybridization conditions. The loss of fidelity can also lead to difficulty in interpreting the data.
>
> Photolithography is a method used by Affymetrix in California to produce in situ arrays using procedures that are similar to those used in the semi-conductor industry. In procedure described by Fodor et al. from Affymetrix U.S. Pat. No. 5,405,783, a photo-deprotection step is used where the protecting group on the phosphoramidite is removed by exposing a photosensitive protecting group to light. Four photo masks are used to create patterns to de-protect areas of the substrate and then a nucleotide is added to these regions. This technique requires four masks for each layer of nucleotides. While this technique allows for the production of high-density oligonucleotide arrays, it is less efficient than traditional phosphoramidite synthesis chemistry. With efficiencies of about 90 to 95 percent, the percentage of full-length oligonucleotides within a feature is further reduced to about 9 to 27 percent for oligonucleotides that are 25 nucleotides long (0.90^{25} to 0.95^{25}).

At column 40 of Jones (US Patent 5,858,671) the inherent obstacle in synthesizing oligonucleotide arrays is disclosed. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69} = 0.50$)." In the present case, applicant is claiming a product that would be the result of an infinite number of couplings, not just 69 as described above.

As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

26. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

Response to argument

At page 14 of the response applicant asserts that the issues recognized in the documents cited are dated and are to be ignored. Applicant directs attention to documents cited in the disclosure and for which one is to rely upon as being "much more germane."

The above argument has been considered and has not been found persuasive. At page 52 of the disclosure applicant does direct attention to several patent documents as disclosing the state of the art. For convenience, the patents, and their issue date, filing date and priority date are all reproduced below.

Patent No. cited	Page	Issued	Filed	Priority
6600031	52	7/29/03	4/21/98	6/7/89
6326489	52	12/24/01	8/5/97	
6548021	52	4/15/03	8/11/98	10/10/97
5807522	52	9/15/98	6/7/95	6/17/94
5744305	52	4/28/98	6/6/95	6/7/89
5143854	52	9/1/92	3/7/90	6/7/89

The instant application was filed 30 November 2005. Clearly, the documents cited by applicant attest to the state of the art some 16 years prior to the filing date, and do not take into account the now art-recognized issues. Contrary to the position asserted by applicant, the issues recognized in the documents cited by the Office, while being "3 years before the case at hand" (response at page 14, second paragraph), are in fact highly informative and raise a genuine question of enablement that cannot be dismissed out of hand.

27. At page 13 of the response applicant asserts:

> The specification also teaches precisely how to isolate sequences consisting of accessible regions based on their altered reactivity to a probe of chromatin structure (e.g., pages 13 and 24-39). Moreover, the specification, in view of the state of the art at the time of filing, teaches how to make arrays comprising these sequences consisting of accessible regions (e.g., pages 51 et seq. and references cited therein) and how to use these arrays for high-throughput screening (e.g., Section VI. Applications beginning on page 55, including for example, identification of binding sites for regulatory proteins, identification of sequence targets, RegDNA chip profiling, chromatin epigenome profiling, etc.). (Emphasis in the original.)

The above argument has been considered and has not been found persuasive. While the specification does make general statements as to how or for what the array could be used for, the specification does not set forth any reaction conditions and specific starting materials that enabled the use of the claimed genus of arrays for any purpose. It is well established that

applicant cannot rely solely upon the state of the art for enablement, and that absent specific reaction conditions and starting materials, undue experimentation is required. *Genentech*. For the above reasons and in the absence of convincing evidence to the contrary, the rejection of claims 2-5 under 35 USC 112, first paragraph, as being non-enabled, is maintained.

28. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

29. Claims 2-5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility.

30. It is noted with particularity that the claimed array is defined in terms of a product-by-process. While such claim format is permissible, the claim must still be directed to a product that has utility. However, not all nucleic acids have utility. An example of such are expressed sequence tags (ESTs) for which no known utility exists. The claimed array does not differentiate between those nucleic acids that do and do not have utility.

31. Acknowledgement is made of where applicant has provided a listing of potential utilities at page 53 of the specification. Such asserted utilities are not deemed to be specific to the members of the array.

32. It matters not whether the claim is drawn to a product or process; the claim must be drawn to an invention that satisfies the utility requirements as set forth under 35 USC 101 and as further developed in the Utility Guidelines. In support of this position, attention is directed to *Brenner, Comr. Pats. v. Manso*n, 148 USPQ 689 (US Sup Ct 1966):

> Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility, creates a monopoly of knowledge which should be granted only if clearly commanded by the statute. Until the process claim has been reduced to production of a product shown to be useful, the metes and bounds of that monopoly are not capable of precise delineation. It may engross a vast, unknown, and perhaps unknowable area. Such a patent may confer power to block off whole areas of scientific development, 22 without compensating benefit to the public. The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
>
> * * *
>
> We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing, a different set of rules was meant to apply to the process which yielded the unpatentable product. 24 That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.
>
> This is not to say that we mean to disparage the importance of contributions to the fund of scientific information short of the invention of something "useful," or that we are blind to the prospect that what now seems without "use" may tomorrow command the grateful attention of the public. But a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.

33. Claims 2-5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Response to argument

34. At page 14, bridging to page 15, of the response, argument is presented that the utility rejection is improper and should be withdrawn as applicant has asserted a utility for the claimed invention and that the assertion of "any particular practical purpose" is sufficient.

35. The above argument has been considered and has not been found persuasive. While agreement is reached in that the specification does provide a general listing of hoped-for utilities, the listing of utilities is not specific for any particular sequence, much less for any specific member for an array. As set forth above, the specification does not identify any array member in terms of its nucleotide sequence or in terms other that it being derived from a probe-accessible region of cellular chromatin. The aspect of listing potential utilities for a class of nucleic acids does not constitute a specific utility for any one member of the array.

36. Argument is presented at page 15 that "the claims are not directed to nucleic acids generally" (emphasis in the original). However, the claims fairly encompass a vast and unknowable class of molecules that in one cell of one organism they may be accessible yet in another cell, be it from the same or different organism may not be accessible. Indeed, the manner by which the nucleic acid is deemed to be "accessible" or not is open to interpretation such that the clams fairly encompass virtually any nucleic acid. See rejection of claims under 35 USC 112, second paragraph, infra.

37. For the above reasons, and in the absence of convincing evidence to the contrary, claims 2-5 remain rejected under 35 USC 101 and 112, first paragraph, as being directed to an invention that lacks a specific, substantial, and credible asserted utility, or a well-established utility.

38. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

39. Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

40. The term "accessible regions" in claim 2 is a relative term which renders the claim indefinite. The term "accessible regions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Acknowledgement is made of the specification providing a definition of the terms at page 12. Said definition, however, is exemplary and not binding. Accordingly, the metes and bounds of the claim cannot be readily determined.

Response to argument

41. At page 16, bridging to page 17, of the response argument is presented that the expression would be known by one of skill in the art. However, there is no evidence of record to support this conclusion. Attention is directed to MPEP 2145.

> Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art.
> The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration.

42. At page 17 of the response applicant reproduces a passage of the specification that provides a definition of the term. The cited passage, while providing a definition as to what it

could be, does not establish the metes and bounds of the expression. In short, one would not be able to determine which nucleic acids actually are encompassed by the claim and which are not as the conditions under which the reaction is to take place are not defined. It is further noted that the claims seemingly encompass nucleic acids that in one case may be non-accessible, yet under evaluation from a different tissue type and/or organism (or reaction condition), may now be construed as being accessible. With such ambiguous language, the metes and bounds of the clams cannot be determined. Therefore, and in the absence of convincing evidence to the contrary, the rejection of claims 2-5 under 35 USC 112, second paragraph, is maintained.

Claim Rejections - 35 USC § 102

43. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

44. Claims 2-5 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 6,153,379 (Caskey et al.).

45. For purposes of examination, the expression "accessible regions of cellular chromatin" has been construed as encompassing not only naturally-occurring chromosomes, but also artificial chromosomes. Further, the aspect of what constitutes "accessible regions" has been construed as encompassing virtually any portion of the chromosome. While page 12 of the specification does provide a definition, said definition is general in terms and not binding.

Accordingly, the polynucleotide sequences on the array can be from virtually any source, of any nucleotide composition, including artificial polynucleotide sequences.

46. Caskey et al., column 4, penultimate paragraph, teach that arrays of oligonucleotide primes can be synthesized and that the oligonucleotide primers can range from 'about 7 to about 30 nucleotides" in length.

47. Caskey et al., column 4, last paragraph, bridging to column 5, first paragraph, teach, "The array includes oligonucleotide primers comprising all possible N-mers." Such a showing is deemed to meet a limitation of each of claims 2-5.

48. For the above reasons, and in the absence of convincing evidence to the contrary, claims 2-5 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent 6,153,379 (Caskey et al.).

Response to argument

At page 17, bridging to page 18, of the response argument is presented that the rejection must be withdrawn, as the array members of Caskey et al., would encompass members that are not derived from a probe-accessible region of cellular chromatin.

This argument has been considered and has not been found persuasive. As set forth above, the chromosome from which the nucleic acid is to be derived has been construed as encompassing artificial chromosomes, which can have any nucleotide sequence of interest. Further, the conditions under which the nucleic acid sequence is deemed to be accessible, or not, is open to interpretation. Accordingly, there is nothing in the claims that would preclude the array members from encompassing literally any nucleic acid molecule- regardless of nucleotide composition, length, or origin.

49. Accordingly, the rejection is deemed proper and is maintained.

Conclusion

50. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.

51. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

52. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

53. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

54. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

55. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/
Primary Examiner, Art Unit 1634